42. (New) The method of claim 1 or 24, wherein the compound has an IC_{50} of at least about 0.001 to about 10mM in a standard *in vitro* assay for measuring the subject protein.

42 Sub. B Contd

43. (New) The method of claim 28, wherein the subject protein is one or more of heat shock protein 70 (hsc70).

REMARKS

Support for the amendments and new claims can be found throughout the disclosure including the Drawings and claims as originally filed.

Particular support for the amendment to claims 1, 5, 24, and 34 can be found at pg. 5, lines 3-6; pg. 17, lines 1-21; pgs. 18-19 (disclosing compounds with unsaturated carbon chains). Additional support for the amendment to claim 1 is provided at pg. 4, lines 19-23.

The amendments to claims 8, 23, 25, and 29 are intended to improve claim clarity and/or dependency. The amendments were not made for any reason relating to patentability.

New claims 42 and 43 were re-written from the second occurrence of claims 28 and 29, respectively.

No new matter has been added by virtue of the amendments or new claims.

Claim 29 was objected to at pg. 2 of the Action. The objection has been addressed.

Claims 1-12, 23, 25-33 stand rejected under 35 USC §112, first paragraph, as not being enabled by the specification as filed. Applicants respectfully disagree with the rejection.

As an initial matter, it appears that the Office deemed the specification enabling for treating some diseases, however what those diseases are is not apparent from the Action at pg. 3, paragraph 5. Clarification is requested.

Applicants believe the rejection has been addressed by this submission.

In particular, the invention is one of broad application that can be used to treat or prevent a wide range of conditions impacted by incorrect protein folding. Specification at pg. 4, lines 19-23. Specific examples of such disorders include disorders afflicting the nervous, hepatic or respiratory systems. Additionally specific conditions are provided at pgs. 4-5, bridging paragraph, and throughout the instant specification.

Especially as amended, the invention of claim 1 fully satisfies the *Wands* factors pointed out by the USPTO at pg. 3.

Applicants respectfully disagree with the rejection on an additional ground.

At pgs. 5-6 of the Action, the USPTO took the position that the claimed invention is obvious. It is not seen how the Office can also allege that Applicants' disclosure is not enabling in view of that position.

Accordingly, reconsideration and withdrawal of the rejection are requested.

Claims 23, and 30-31 stand rejected under 35 USC §112, second paragraph, on various grounds. The rejection has been addressed by this submission.

Claims 1-12, 14-15, and 22-34 stand rejected as obvious over Herron (US Pat. 4,764,521), Rubenstein (*Am. J. Respir. Crit. Care Med.* 157: 484 (1998); and Welchter et al. (US. Pat. NO. 5,981, 592). Applicants must respectfully disagree.

Claims 1, 5, 24, and 34 have been amended to point out that the recited carbocyclic aryl compounds includes an unsaturated carbon chain. As cited, the references do not teach, suggest or provide any incentive to use such a compound in a method to treat cystic fibrosis or any other disorder as provided in Applicants' specification.

As relied on, Rubenstein discloses an FDA approved drug for the management of urea cycle disorders and cystic fibrosis ie., sodium 4-phenylbutyrate (Buphenyl or 4PBA). Rubenstein does not teach, suggest or provide any motivation to use Applicants' compound with an unsaturated carbon chain, either alone or together with the other cited references.

Rubenstein states that 4PBA is an FDA approved drug. Thus, workers in the field would have been particularly dissuaded from modifying it in the way suggested by the PTO. To do so would have subjected the Office's modified 4PBA to expensive and time consuming clinical trials. There is nothing in the cited references that would motivate workers to do this. Loss of FDA approval is to be avoided in this field.

As cited, Herron discloses use of certain substituted aryl carboxylic acids for the treatment of cystic fibrosis. However, Herron does not provide for Applicant's method of employing a carbocyclic aryl compound with an unsaturated carbon atom. Rubenstein and Welchter, as relied on, does not remedy this defect.

More specifically, there is absolutely no teaching or suggestion in the cited art to remove substituents from the aromatic ring of Herron's compounds. Rubenstein does not teach, suggest or provide any motivation to do this as alleged by the Office. If anything, Rubenstein *teaches away* from modifying 4PBA at all. See Rubenstein at pg. 488, col. 2 .

Welchter, as cited, simply does not teach, suggest or provide any motivation to use any carbocyclic aryl compound with an unsaturated carbon chain in Applicants' treatment method either alone or in combination with the other cited references.

Unlike the cited references, it was Applicants who discovered that the claimed invention provided advantages over prior compounds, particularly 4PBA. As claimed, the invention employs unsaturated compounds that can be administered at lower doses, are more stable *in vivo*, have higher bioavailability, and lend themselves to better solubility and formulation. See pages 5-6 of the specification.

None of those substantial advantages are taught or suggested by the Herron, Rubenstein and Welchter citations.

In view thereof, reconsideration and withdrawal of the §103 are requested.

On pg. 2, paragraph 3, the USPTO indicated that the claims have been examined insofar as they read on a method for treating cystic fibrosis. Applicants fully expect the Office to expand the search beyond the elected condition once there is indication of allowable subject matter.

On October 30, 2000, Applicants submitted a Supplemental IDS. The USPTO received the IDS on November 2, 2000 as indicated by the attached postcard copy. There is no indication that the Supplemental IDS has been considered by the Examiner. As a courtesy, the present submission includes a copy of the prior IDS submission. Consideration of the IDS is requested.

Although it is not believed that any fee is needed to consider this submission including the resubmission of the Supplemental IDS, the undersigned authorizes the Examiner to charge Deposit Account No. **04-1105** should such fee be deemed necessary.

Should the Examiner wish to discuss any of the amendments and/or remarks made herein, the undersigned attorney would appreciate the opportunity to do so. Thus the Examiner is hereby authorized to call the undersigned, collect at the number shown below.

Attached to this submission is a marked-up version of the changes made to the specification and claims. The attached page is captioned "version with markings to show changes made".

Respectfully submitted,

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Date: 2 October 2002

VERSION WITH MARKINGS TO SHOW CHANGES MADE

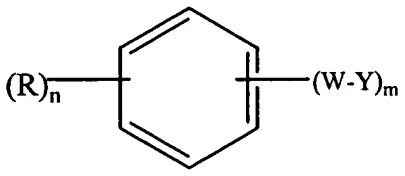
IN THE CLAIMS:

Claim 11 has been canceled without prejudice. The second occurrence of claims 28 and 29 has also been canceled.

Claims 1, 5, 8, 23-25, 29, and 34 have been amended as follows:

1. (Amended) A method for treating a disease or condition modulated by protein expression in a mammal suffering from, susceptible to, or recovering from the disease or condition, the method comprising administering to the mammal a therapeutically effective amount of at least one carbocyclic aryl compound comprising an unsaturated carbon chain and having spaced from the aryl ring a substituent of carboxy acid, ester, sulfonic acid, nitro, cyano or haloalkyl; or a pharmaceutically acceptable salt thereof, wherein the disease or condition afflicts or is suspected of afflicting the nervous, hepatic, or respiratory system.

5. (Amended) The method of claim 1 wherein the compound is of the following Formula I:



I

wherein each W is independently optionally substituted alkylene; optionally substituted alkenylene; optionally substituted alkynylene; optionally substituted heteroalkylene; optionally substituted heteroalkenylene; or optionally substituted heteroalkynynylene and further wherein W comprises an unsaturated straight carbon chain;

each Y is independently a carboxy acid, ester, sulfonic acid, nitro, cyano or haloalkyl;

each R is independently halogen, cyano, nitro, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl;

m is an integer of from 1 to 6; n is an integer of from 0 to 5; and pharmaceutically acceptable salts thereof, with the exclusion of 4-phenylbutyric acid.

8. (Amended) The method of claim 5 [7], wherein the compound further comprises a phenyl ring in the fourth position of the chain.

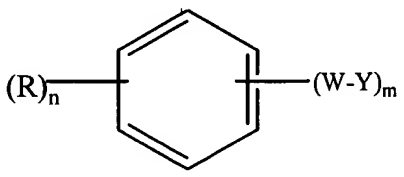
23. (Amended) The method of claim 22 [23], wherein the compound is administered to the mammal orally, intramuscularly or intraperitoneally.

24. (Amended) A method for treating a mammal suffering from, susceptible to, or recovering from cystic fibrosis (CF), the method comprising administering to the mammal a therapeutically effective amount of at least one carbocyclic aryl compound comprising an unsaturated carbon chain and having spaced from the aryl ring a substituent of carboxy acid, ester, sulfonic acid, nitro, cyano or haloalkyl compound; or a pharmaceutically acceptable salt thereof.

25. (Amended) The method of [any one of claims 1-24] claim 1 or 24, wherein the compound increases or decreases expression of a subject protein by at least about 10% in a standard *in vitro* assay for measuring the subject protein.

29. (Amended) The method of claim 28 [29], wherein the compound exhibits an IC_{50} of about 100 μm or less in the assay.

34. (Amended) A method for treating a human subject suffering from, susceptible to, or recovering from a disease or condition associated with surfactant protein C, cystic fibrosis (CF) α1 anti-trypsin disease, Alzheimer's disease, Marfan syndrome, familial hypercholesterolemia, or Tay-Sachs disease, the method comprising administering to the human subject a therapeutically effective amount of compound is of the following Formula I:



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wherein each W is independently optionally substituted alkylene; optionally substituted alkenylene; optionally substituted alkynylene; optionally substituted heteroalkylene; optionally substituted heteroalkenylene; or optionally substituted heteroalkynynylene and further wherein W comprises an unsaturated straight carbon chain;

each Y is independently a carboxy acid, ester, sulfonic acid, nitro, cyano or haloalkyl;

each R is independently halogen, cyano, nitro, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl;

m is an integer of from 1 to 6; n is an integer of from 0 to 5; and pharmaceutically acceptable salts thereof, with the exclusion of 4-phenylbutyric acid.

The following new claims 42 and 43 have been added.

42. (New) The method of claim 1 or 24, wherein the compound has an IC_{50} of at least about 0.001 to about 10mM in a standard *in vitro* assay for measuring the subject protein.

43. (New) The method of claim 28, wherein the subject protein is one or more of heat shock protein 70 (hsc70).

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